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| Applicant(s) | : | Attila T. LÖRINCZ, et al. | Group Art Unit: 1631 |
| Serial No | : | 09/210,031 | Examiner: BRUSCA, J. |
| Filed | : | December 11, 1998 | |
| For | : | UNIVERSAL COLLECTION MEDIUM | |

**DECLARATION UNDER 37 C.F.R. §1.132**

Commissioner of Patents
Washington, D.C. 20231

Sir:

This is a Declaration filed pursuant to 37 C.F.R. §1.132.

I, the undersigned, Attila T. Lörincz, Ph.D., declare and state that:

1. I am a co-inventor of the subject patent application having serial no. 09/210,031.

2. My education and professional experience as an expert in the area of nucleic acid chemistry and analysis are set forth on the attached copy of my Curriculum Vitae.

3. As stated on my Curriculum Vitae attached herewith, my area of expert training and experience is in nucleic acid chemistry, in the analysis of nucleic acids in biological samples, and in the use of such nucleic acid analyses to develop diagnoses and prognoses concerning diseases related to the organism from which the nucleic acid was obtained.

4. I understand that the Examiner considers the composition described in the above-identified application obvious in view of the composition reported at column 6, lines 8-61 and in Example 4 of Dunphy U.S. Patent No. 5,679,333 ("'333 patent").

5. It is my opinion, as an expert in the field of nucleic acid chemistry analysis, that the composition described in Dunphy does not teach or suggest the compositions described in the above-identified application because the direct analysis of cells by both cytological analysis and molecular analysis of DNA, RNA, or protein is not possible using the compositions of Dunphy.

6. To support this position, I present evidence herein establishing that the Dunphy composition of Example 4 does not properly preserve DNA and RNA. The data demonstrate that the Dunphy composition cannot provide direct molecular analysis of cells according to the subject claims because the Dunphy composition quickly degrades the nucleic acids in the sample.

7. The following experimental study measures the stability of nucleic acids in our universal collection medium (UCM) composition as compared to nucleic acid samples in the Dunphy composition over a period of four weeks. In this study, eight (8) different formulations were evaluated for their ability to maintain cellular DNA and cellular RNA. This study demonstrates that Dunphy's formulations, with or without the addition of EDTA or other modifications, are not suitable storage media for the analysis of cellular nucleic acids. Low levels of DNA or RNA detection in Dunphy's formulations even in the Day 1 timepoint suggest that Dunphy's tissue fixative media are not appropriate for analyzing nucleic acids. All of the applicants' (UCM) formulations evaluated in this study are suitable media for the storage and subsequent detection of cellular nucleic acids.

8. The 8 formulations, applicants' 1-3 and Dunphy's 4-8, were prepared as follows and used in the molecular analyses described below:

Formulation No. 1 is formulation 130 from the UCM I patent application (USSN: 09/210,031; "UCM I"). It shows the ability of the UCM formulation containing glutaraldehyde to preserve cellular DNA and RNA.

| | |
|---|---|
| Butanol | 7% v/v |
| Sodium Azide | 0.05% w/v |
| EDTA | 0.18% w/v (= 5 mM) |
| Glutaraldehyde-Sodium-Bisulfate (G-S-B) | 2.5% w/v |
| Acetic Acid | 0.11% v/v |
| pH 3.7 | |

Formulation No. 2, similar to Formulation No. 1 above, but without the addition of glutaraldehyde, shows the need for a cross-linker in the UCM formulation.

| | |
|---|---|
| Butanol | 7% v/v |
| Sodium Azide | 0.05% w/v |
| EDTA | 0.18% w/v (= 5 mM) |
| Acetic Acid | 0.11% v/v |
| pH 3.7 | |

Formulation No. 3, UCM similar to Formulation No. 1 above, but without the addition of EDTA, shows the need for a chelating agent in "UCM I," to assist in the inhibition of RNA and DNA degradation.

| | |
|---|---|
| Butanol | 7% v/v |
| Sodium Azide | 0.05% w/v |
| Glutaraldehyde-Sodium-Bisulfate (G-S-B) | 2.5% w/v |
| Acetic Acid | 0.11% v/v |
| pH 3.7 | |

Formulation No. 4 is Dunphy's tissue fixative from Example 4 of the Dunphy '333 patent. It is one of five variations of Dunphy's media that tests its ability to preserve cellular DNA and RNA.

| | |
|---|---|
| Ethanedial (Glyoxal) | 3.75% v/v |
| Ethanol | 20% v/v |
| PEG (MW 8000) | 2.0% w/v |
| Ethylene Glycol | 0.75% v/v |
| Ethanoic Acid | 0.75% v/v |
| Dimethyl Sulfoxide (DMSO) | 0.0275% v/v |

Formulation No. 5 of Dunphy's tissue fixative is similar to Formulation No. 4 above with the addition of EDTA at the concentration used in the Dunphy pre-injection and arterial injection fluids. The Examiner stated that it would have been obvious to add EDTA in formulations of Dunphy's media. This shows that EDTA does not improve nucleic acid stability. *See* Tables 2 and 4.

| | |
|---|---|
| Ethanedial (Glyoxal) | 3.75% v/v |
| Ethanol | 20% v/v |
| PEG (MW 8000) | 2.0% w/v |
| Ethylene Glycol | 0.75% v/v |
| Ethanoic Acid | 0.75% v/v |
| Dimethyl Sulfoxide (DMSO) | 0.0275% v/v |
| EDTA | 0.08% w/v |

Formulation No. 6 of Dunphy's tissue fixative is similar to Formulation No. 4 above with the addition of EDTA at the concentration used in the UCM formulations. This shows that EDTA does not improve nucleic acid stability, regardless of its concentration. *See* Tables 2 and 4.

| | |
|---|---|
| Ethanedial (Glyoxal) | 3.75% v/v |
| Ethanol | 20% v/v |
| PEG (MW 8000) | 2.0% w/v |
| Ethylene Glycol | 0.75% v/v |
| Ethanoic Acid | 0.75% v/v |
| Dimethyl Sulfoxide (DMSO) | 0.0275% v/v |
| EDTA | 0.18% w/v (= 5 mM) |

Formulation No. 7 of Dunphy's tissue fixative is similar to Formulation No. 4 above with the addition of phosphate buffer to raise the pH to approximately 7.0. The Dunphy patent states that although the solution typically has an acidic pH, it may be buffered to a substantially neutral pH. Addition of the phosphate buffers raises the pH of the solution to a neutral range. *See* Tables 2 and 4.

| | |
|---|---|
| Ethanedial (Glyoxal) | 3.75% v/v |
| Ethanol | 20% v/v |
| PEG (MW 8000) | 2.0% w/v |
| Ethylene Glycol | 0.75% v/v |
| Ethanoic Acid | 0.75% v/v |
| Dimethyl Sulfoxide (DMSO) | 0.0275% v/v |
| Acid Sodium Phosphate Monohydrate | 0.4% w/v |
| Disodium Phosphate (Anhydrous) | 0.65% w/v |
| pH 6.8-7.8 | |

Formulation No. 8 of Dunphy's tissue fixative is similar to Formulation No. 4 above with the addition of phosphate buffer to raise the pH to an approximately neutral range, as well as the addition of EDTA. The addition of EDTA at the concentration used in the Dunphy pre-injection and arterial injection fluids shows that it does not improve nucleic acid stability when included in a neutral formulation of Dunphy's media. *See* Tables 2 and 4.

| | |
|---|---|
| Ethanedial (Glyoxal) | 3.75% v/v |
| Ethanol | 20% v/v |
| PEG (MW 8000) | 2.0% w/v |
| Ethylene Glycol | 0.75% v/v |
| Ethanoic Acid | 0.75% v/v |
| Dimethyl Sulfoxide (DMSO) | 0.0275% v/v |
| Acid Sodium Phosphate Monohydrate | 0.4% w/v |
| Disodium Phosphate (Anhydrous) | 0.65% w/v |
| EDTA | 0.08% w/v |
| pH 6.8-7.8 | |

9. Cultured, Human Papilloma Virus (HPV)-16-positive CaSki cells and HPV-negative Jurkat cells were used to examine whether or not the Dunphy compositions preserve and make possible the direct analysis of nucleic acid.

10. Samples for DNA analysis were prepared as follows: 1.5 mL bulk samples were made from which 200 µL, single use aliquots were made. The aliquots were stored at room temperature until tested.

Positive Control: HPV16 plasmid DNA was spiked into each of the eight formulations at a final concentration of 50 pg/mL.

Negative Control: A culture of HPV negative cells (obtained from ATCC cat #. TIB-152) was isolated and spiked into each of the eight

formulations at a concentration of $10^6$ cells/mL of each formulation.

CaSki Cells: A culture of HPV positive cells (obtained from ATCC cat# CRL-1550) was isolated and spiked into the eight formulations at two different concentrations, $10^4$ and $10^5$ cells/mL.

11. Samples for RNA Analysis were prepared as follows: 1 mL bulk samples were made from which 40 µL, single use aliquots were made. The aliquots were stored at room temperature until tested.

Positive Control: HPV16 *in vitro* transcribed RNA was spiked into each of the eight formulations at a final concentration of 11 pg/mL.

Negative Control: A culture of HPV negative cells (obtained from ATCC cat #. TIB-152) was isolated and spiked into each of the eight formulations at a concentration of $10^6$ cells/mL of each formulation.

CaSki Cells: A culture of HPV positive cells (obtained from ATCC cat# CRL-1550) was isolated and spiked into the eight formulations at two different concentrations, $10^5$ and $10^6$ cells/mL.

12. Samples were prepared and aliquotted, stored overnight at room temperature and tested the following day. The Day 1 time point reflects the handling of a true patient sample. Samples are usually collected and shipped to a testing facility. Therefore, the earliest that a patient sample could be tested would be 12 to 24 hours after the sample was collected.

13. The estimated time for conducting DNA and RNA stability assays was 5-6 hours for 2 people and was conducted as follows:

Isolating cell cultures (1 hour)
Counting cell cultures (15 minutes)
Spiking cells into formulations (1 hour)
Spiking control into formulation (15 minutes)
Aliquotting
Vortexing (30 sec per sample, 130 samples, ~ 1.5 hours)
Pipetting into labeled tubes
Organizing samples for testing (30 minutes)

14. The direct analyses of nucleic acids were conducted by following the method for detecting DNA and RNA by the Digene Hybrid Capture (HC) method, described in WO 93/10263 by Digene Corporation.

15. The UCM DNA stability assay (estimated assay time: 4-5 hrs) was performed by first preparing the plate controls according to the package insert. Denaturation reagent (Sodium hydroxide; 100 µl) was added to each of the samples and all of the samples were denatured at 65°C for 45 minutes. After incubation, the samples were neutralized by adding 100 µl of probe, containing an RNA probe specific to genomic HPV DNA, and transferring 100 µl of each sample in triplicate to the hybridization plate. Hybridization occurred at 65°C for 1 hour. Anti-hybrid detection antibody, DR-1, (25 µl) was added to each well and all 125 µl of the mixture was transferred to the capture plate containing strepavidin-coated microplate coated with anti-hybrid polyclonal antibody. The sample was captured for 1 hour at room

temperature while shaking at 1100 rpm. The plate was then washed and blotted. The chemiluminescent substrate detection reagent was added to the plate which was then covered and stored in the dark for 30 minutes. The plate was then read on a luminometer. The data were then expressed as a signal-to-noise ratio. These assays test the efficacy of preservation media as specific signal is obtained only when DNA or RNA is not degraded, since signal is contingent upon the hybridization of probes to non-degraded DNA or RNA.

16. The UCM RNA stability assay was performed by first adding an equal volume of freshly prepared 2X SDS-based lysis buffer plus proteinase K to each sample. Lysis occurred at 37°C for 30 minutes in a waterbath. Lysis buffer without Proteinase K and without calcium (1X; 160 µl) was added to each of the samples. Plate control (480 µl) was added to the samples and vortexed well. Each sample (60 µl) was aliquotted in triplicate on the hybridization plate. The UCM probe, containing single-stranded DNA biotinylated probe specific for HPV E6 and E7 RNA (50 µl) was then added to each well and hybridized for 2 hours in a 65°C heat block. DR-1 (25 µl) was added to each well and the entire sample was transferred to the streptavidin capture plate. Capture occurred at room temperature for 1 hour while shaking at 1100 rpm. The plate was then washed and blotted dry. The plate was then heat washed at 53°C for 45 minutes, followed by washing and blot drying as previously described. Detection reagent to the plate which was then covered and stored in the dark for 30 minutes. The plate was then read on a luminometer with a standard setting. The data were then expressed as a signal-to-noise ratio. These assays test the efficacy of

preservation media as specific signal is obtained only when DNA or RNA is not degraded, since signal is contingent upon the hybridization of probes to non-degraded DNA or RNA.

17. On the day of testing, a single tube for each of the controls and cellular samples was used in each assay. Each tube contained sufficient sample for triplicate assays of the nucleic acid targets. The raw data are represented in Relative Light Units (RLUs) that were collected on Digene's standard Luminometer. Hybrid Capture nucleic acid assays normally have less than or equal to 25% coefficient of variation (%CV) within triplicate assays. When the %CV is greater than 25%, one outlier may be eliminated. The compiled data are presented as signal/noise (S/N) where the signal represents the average RLU of the triplicate assays divided by the noise obtained from a buffer only, negative control.

18. Tables 1 and 2 and Figures 1A-1D set forth the data resulting from the DNA stability assay experiments.

| | STORAGE MEDIA # | POSITIVE CONTROLS (50PG/ML HPV16 DNA) | | | | HPV NEGATIVE CELLULAR SAMPLES ($10^6$ JURKAT CELLS/ML) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | DAY 1 | WEEK 2 | WEEK 3 | WEEK 4 | DAY 1 | WEEK 2 | WEEK 3 | WEEK 4 |
| UCMI | 1 | 93.2 | 46.9 | 33.6 | 24.9 | 1.8 | 1.4 | 1.3 | 1.5 |
| | 2 | 82.8 | 9.3 | 6.1 | 3.2 | 1.7 | 2.0* | 1.5 | 1.4 |
| | 3 | 75.0 | 28.5 | 18.1 | 11.3 | 1.4 | 1.4 | 1.2 | 1.2 |
| DUNPHY'S | 4 | 1.0 | 1.0 | 0.0 | 0.9 | 1.0 | 1.1 | 0.0 | 0.9 |
| | 5 | 0.9 | 0.6 | 1.1 | 1.0 | 0.9 | 0.8 | 1.2 | 0.9 |
| | 6 | 0.9 | 2.8* | 1.0 | 1.2 | 0.8 | 0.9 | 1.0 | 1.0 |
| | 7 | 1.0 | 1.0 | 1.4 | 1.0 | 0.9 | 1.0 | 1.3 | 1.0 |
| | 8 | 0.9 | 0.9 | 0.9 | 0.9 | 1.3 | 1.0 | 1.2 | 1.2 |

* Indicates outliers that are the result of incomplete denaturation of the samples.

Table 1: The Signal to Noise (S/N) values for the Hybrid Capture II HPV DNA assays performed at each of the nucleic acid study time points for the positive and HPV negative controls. The storage media number refers to the formulation number identified previously. Media 1-3 are UCM formulations, while media 4-8 are Dunphy's formulations.

FIGURE 1(A):

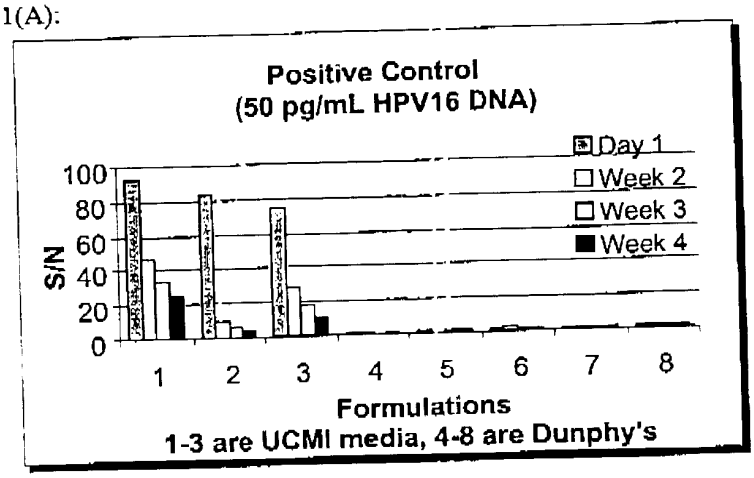


Figure 1(A) shows the results of the Signal to Noise (S/N) values (y-axis) of the positive control in each of the eight formulations, where the Hybrid Capture II HPV DNA assays were performed at each of the nucleic acid study time points.

FIGURE 1(B):

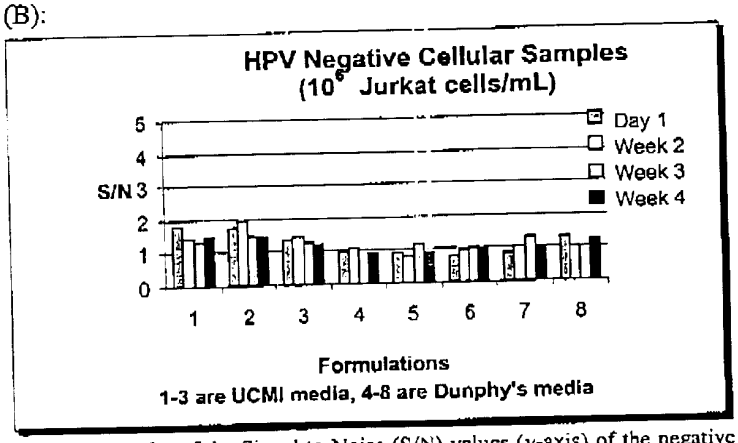


Figure 1(B) shows the results of the Signal to Noise (S/N) values (y-axis) of the negative control ($10^6$ Jurkat cells/mL) in each of the eight formulations, where the Hybrid Capture II HPV DNA assays were performed at each of the nucleic acid study time points.

| | STORAGE MEDIA # | HPV POSITIVE CELLULAR SAMPLES ($10^4$ CASKI CELLS/ML) | | | | HPV POSITIVE CELLULAR SAMPLES ($10^5$ CASKI CELLS/ML) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | DAY 1 | WEEK 2 | WEEK 3 | WEEK 4 | DAY 1 | WEEK 2 | WEEK 3 | WEEK 4 |
| UCM 1 | 1 | 25.4 | 46.0 | 38.5 | 40.8 | 312.1 | 365.2 | 438.1 | 270.0 |
| | 2 | 99.4 | 57.8 | 50.4 | 37.0 | 652.7 | 621.7 | 569.2 | 356.0 |
| | 3 | 31.8 | 28.2 | 29.4 | 22.7 | 223.4 | 325.0 | 242.6 | 180.2 |
| DUNPHY'S | 4 | 1.0 | 1.0 | 0.0 | 0.9 | 1.0 | 1.1 | 0.0 | 1.0 |
| | 5 | 1.0 | 0.5 | 1.1 | 1.0 | 0.9 | 0.6 | 1.1 | 1.0 |
| | 6 | 0.9 | 1.1 | 0.9 | 1.1 | 0.8 | 1.0 | 0.9 | 1.1 |
| | 7 | 0.9 | 1.0 | 1.3 | 1.0 | 0.9 | 1.1 | 1.4 | 1.1 |
| | 8 | 1.1 | 1.0 | 1.0 | 1.2 | 1.2 | 1.0 | 1.0 | 1.3 |

* Indicates outliers that are the result of incomplete denaturation of the samples.

Table 2: The Signal to Noise (S/N) values for the Hybrid Capture II HPV DNA assays performed at each of the nucleic acid study time points for the HPV positive samples using $10^4$ or $10^5$ CaSki cells. The storage media number refers to the formulation number identified in the materials and methods. Media 1-3 are UCM formulations, while media 4-8 are Dunphy's formulations.

FIGURE 1(C):

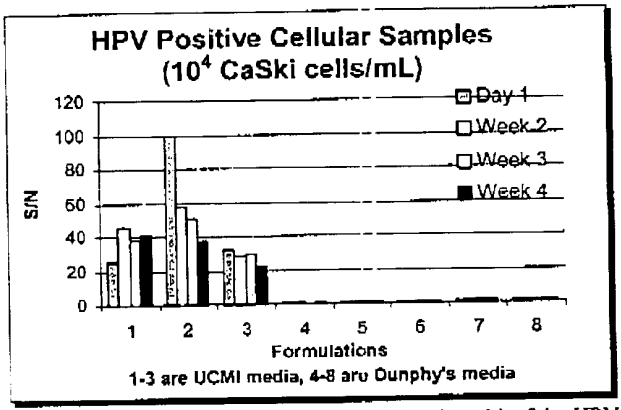


Figure 1(C) shows the results of the Signal to Noise (S/N) values (y-axis) of the HPV positive samples ($10^4$ CaSki cells/mL) in each of the eight formulations, where the Hybrid Capture II HPV DNA assays were performed at each of the nucleic acid study time points.

FIGURE 1(D):

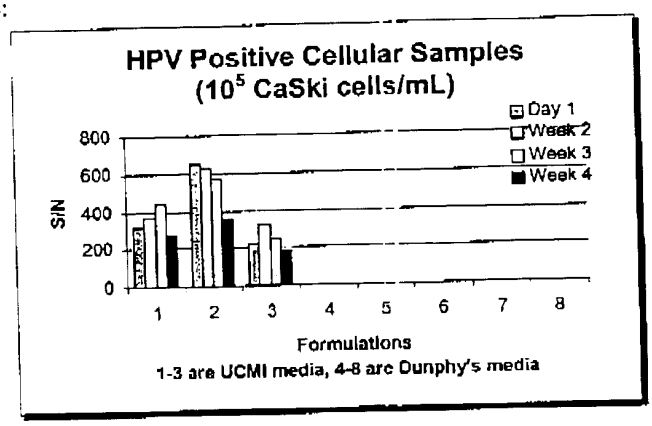


Figure 1(D) shows the results of the Signal to Noise (S/N) values (y-axis) of the HPV positive samples ($10^5$ CaSki cells/mL) in each of the eight formulations, where the Hybrid Capture II HPV DNA assays were performed at each of the nucleic acid study time points.

19. The UCM data from the DNA stability assays provide the following results: UCMI Formulation Nos. 1-3 were evaluated for the use of glutaraldehyde and EDTA to stabilize cellular nucleic acids in UCMI formulations. EDTA variations were introduced to determine if the addition of a chelating agent to Dunphy's media would enhance nucleic acid stability in the media. The positive control HPV16 plasmid DNA spiked into these three formulations gave robust signals at the Day 1 time point, but lost signal over time (Figure 1). These results were expected since UCM formulations are acidic and plasmid DNA is known to be unstable in an acidic environment[1]. The negative control samples had consistent negative signals, as determined as a S/N less than 2.0. As seen in Table 1, there are a few instances where the S/N for the negative control is at or greater than 2.0 (Formulation No. 2, Week 2).

[1] JJ Green, Rao VB. Recombinant DNA Principles and Methodologies. Mercel Dekker, USA 1998, p.23.

This is the result of an incomplete denaturation step for these samples. The denaturation step is crucial for lysing the cells and destroying cellular RNA. If RNA destruction is incomplete, the naturally occurring DNA:RNA hybrids may be captured and detected in this assay (Table 1, Figure 1). The HPV positive cellular samples gave robust signals for these three formulations. The removal of EDTA in Formulation No. 3 resulted in a general decrease in signal throughout the study indicating that the EDTA is essential for the stability of cellular DNA. The absence of the cross-linking agent, glutaraldehyde-sodium-bisulfate (GSB), in Formulation No. 2 gave a stronger signal than Formulation Nos. 1 and 3 which have the agent.

20. The Dunphy data from the DNA stability assays provide the following results: Several different Dunphy formulations (Formulation Nos. 4-8) were examined for their ability as a storage media for cellular DNA and RNA. EDTA was added to Formulation Nos. 5, 6 and 8, and Formulation Nos. 7 and 8 were neutralized in an attempt to stabilize DNA. Dunphy's media are not suitable for nucleic acid storage because they failed in every formulation and at every time point to preserve DNA (Tables 1 and 2; Figures 1A-1D). The addition of EDTA to Dunphy's Formulation Nos. 5, 6, or 8 had no effect on the stability of nucleic acids. See Tables 1 and 2. Neutralizing the pH of Dunphy's media (Formulation Nos. 7 and 8) also failed to stabilize the cellular DNA.

21. Tables 3 and 4 and Figures 2A-2D set forth the data resulting from the RNA stability analyses.

| | STORAGE MEDIA # | POSITIVE CONTROLS (11 PG/ML HPV16 RNA) | | | | HPV NEGATIVE CELLULAR SAMPLES ($10^6$ JURKAT CELLS/ML) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | DAY 1 | WEEK 2 | WEEK 3 | WEEK 4 | DAY 1 | WEEK 2 | WEEK 3 | WEEK 4 |
| UCM I | 1 | 5.6 | 1.2 | 1.1 | 1.0 | 1.1 | 1.0 | 1.2 | 1.7 |
| | 2 | 35.9 | 31.5 | 30.8 | 27.0 | 1.0 | 1.0 | 1.1 | 1.1 |
| | 3 | 7.8 | 1.3 | 0.8 | 1.4 | 1.0 | 1.0 | 0.8 | 0.9 |
| DUNPHY'S | 4 | 1.0 | 0.9 | 1.5 | 0.9 | 0.9 | 0.8 | 1.0 | 1.2 |
| | 5 | 1.2 | 0.6 | 1.2 | 0.8 | 1.1 | 0.6 | 0.8 | 1.0 |
| | 6 | 0.9 | 1.7 | 1.2 | 0.9 | 1.1 | 1.2 | 1.2 | 0.9 |
| | 7 | 1.0 | 1.1 | 1.1 | 1.1 | 1.1 | 1.2 | 0.9 | 1.0 |
| | 8 | 0.9 | 1.2 | 0.8 | 1.4 | 1.1 | 1.1 | 0.9 | 1.2 |

Table 3: The Signal to Noise (S/N) values for the Hybrid Capture II HPV RNA assays performed at each of the nucleic acid stability study time points for the HPV positive samples using $10^4$ or $10^5$ CaSki cells. The storage media number refers to the formulation number identified previously. Media 1-3 are UCM formulations, while media 4-8 are Dunphy's formulations.

FIGURE 2(A):

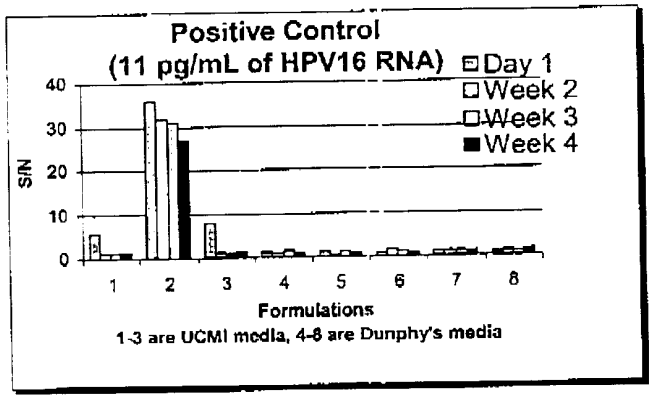


Figure 2(A) shows the results of the Signal to Noise (S/N) values (y-axis) of the positive control in each of the eight formulations, where the Hybrid Capture II HPV RNA assays were performed at each of the nucleic acid study time points.

FIGURE 2(B):

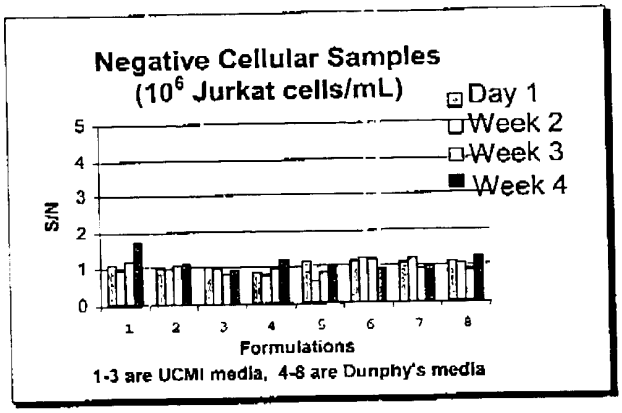


Figure 2(B) shows the results of the Signal to Noise (S/N) values (y-axis) of the negative control in each of the eight formulations, where the Hybrid Capture II HPV RNA assays were performed at each of the nucleic acid study time points.

| | STORAGE MEDIA # | HPV POSITIVE CELLULAR SAMPLES ($10^5$ CASKI CELLS/ML) | | | | HPV POSITIVE CELLULAR SAMPLES ($10^6$ CASKI CELLS/ML) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | DAY 1 | WEEK 2 | WEEK 3 | WEEK 4 | DAY 1 | WEEK 2 | WEEK 3 | WEEK 4 |
| UCM I | 1 | 3.6 | 3.7 | 3.9 | 3.8 | 29.9 | 25.0 | 28.5 | 23.8 |
| | 2 | 2.7 | 2.3 | 2.1 | 2.1 | 21.0 | 21.8 | 11.4 | 14.7 |
| | 3 | 4.6 | 3.2 | 3.3 | 3.3 | 19.8 | 27.8 | 21.8 | 22.0 |
| DUNPHY'S | 4 | 0.9 | 0.9 | 0.9 | 1.2 | 0.9 | 0.8 | 1.1 | 1.4 |
| | 5 | 1.2 | 0.6 | 1.3 | 1.1 | 1.1 | 0.5 | 1.2 | 1.0 |
| | 6 | 0.9 | 1.3 | 1.0 | 1.0 | 1.0 | 1.0 | 1.2 | 1.0 |
| | 7 | 1.2 | 1.3 | 0.8 | 1.0 | 1.2 | 1.2 | 1.2 | 1.3 |
| | 8 | 1.2 | 1.3 | 0.8 | 1.1 | 0.7 | 1.1 | 0.8 | 1.2 |

Table 4: The Signal to Noise (S/N) values for the Hybrid Capture II HPV RNA assays performed at each of the nucleic acid study time points for the HPV positive samples using $10^5$ or $10^6$ CaSki cells. The storage media number refers to the formulation number identified previously. Media 1-3 are UCM formulations, while media 4-8 are Dunphy's formulations.

FIGURE 2(C):

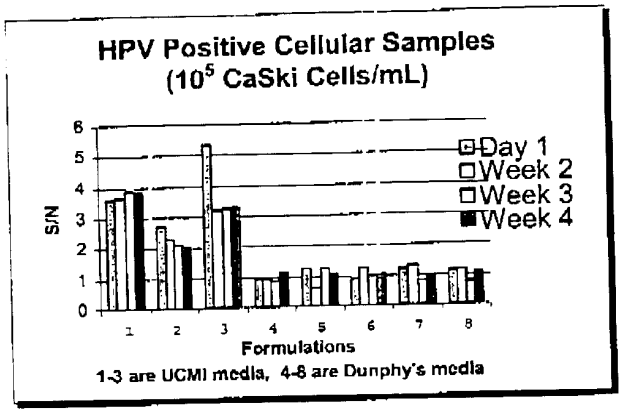


Figure 2(C) shows the results of the Signal to Noise (S/N) values (y-axis) of the HPV positive samples ($10^5$ CaSki cells/mL) in each of the eight formulations, where the Hybrid Capture II HPV RNA assays were performed at each of the nucleic acid study time points.

FIGURE 2(D):

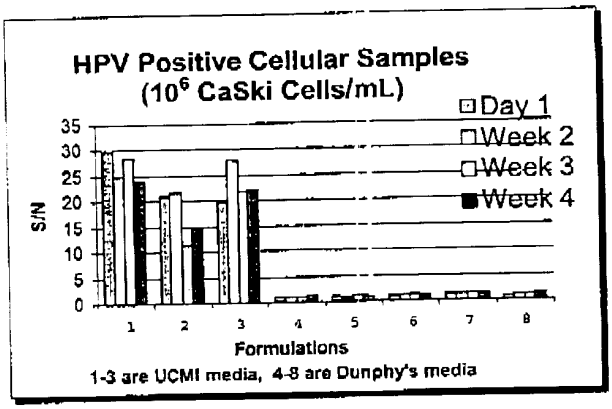


Figure 2(D) shows the results of the Signal to Noise (S/N) values (y-axis) of the HPV positive samples ($10^6$ CaSki cells/mL) in each of the eight formulations, where the Hybrid Capture II HPV RNA assays were performed at each of the nucleic acid study time points.

22. The UCM data from the RNA stability assays provide the following results: The positive control HPV16 RNA spiked into these three formulations gave significantly different results. Only Formulation No. 2, which lacks the cross linking agent (GSB), gave a robust and consistent signal over the course of the study (Tables 3

and 4; Figures 2A-2D). Formulation Nos. 1 and 3 had a weak signal at Day 1 that decreased dramatically over time, indicating that *in vitro* transcribed RNA is not stable in the UCM I formulations that utilize GSB. The negative control performed as expected in these formulations. The HPV positive cellular samples gave consistent signals for these three formulations over time. In general, the samples in Formulation No. 2, where the cross linking reagent was omitted gave lower signals than either Formulation No. 1 or 3. The cross linking agent may help reduce RNase activity and/or stabilize cellular RNA in the cellular samples. The chelating agent, EDTA, is not known to efficiently inhibit RNase activity, therefore the addition of EDTA does not stabilize RNA and no significant decrease was observed between Formulation Nos. 1 and 3.

23. The Dunphy data from the RNA stability assays provide the following results: Dunphy's media are not suitable for nucleic acid storage because they failed in every formulation and at every time point to preserve RNA (Tables 3, 4 and Figure 2). The addition of EDTA to Dunphy's Formulation Nos. 5, 6, or 8 had no effect on the stability of nucleic. Neutralizing the pH of the Dunphy's media (Formulation Nos. 7 and 8) also failed to stabilize the cellular RNA.

24. Thus, all tested compositions based on Dunphy's Example 4 formulation for tissue preservation failed to preserve the HPV DNA or RNA properly, as compared to applicants' UCM formulations. Formulations 4-8 of Tables 2 and 4 and Figures 1 and 2 show that the Dunphy-based compositions are not able to preserve the integrity of cellular DNA or RNA, as the S/N ratios are below 2. In contrast, as

reported in the instant application, the UCM composition properly preserves both the cellular DNA and RNA for hybrid capture assays. The preservation capability of the UCM formulation is apparent as the signal to noise ratio was strongly positive for both DNA and RNA analysis.

25. In contrast to Dunphy's teachings that PEG with a molecular weight between 7000 and 8000 is preferred for stabilizing cellular samples, these experiments demonstrate that glutaraldehyde may be effectively used as a fixative in Digene's UCMI formulations. EDTA is a chelating agent that may reduce DNase activity. These experiments have demonstrated that the addition of EDTA in Digene's UCMI formulations does help to stabilize cellular DNA that is stored at room temperature over a period of four weeks. However, the addition of EDTA to Dunphy's formulations does not stabilize the nucleic acids, as determined by little detectable signal from the HPV positive samples.

26. Since DNA is known to be unstable when stored for longer periods of time in an acidic environment (JJ Green, Rao VB. Recombinant DNA Principles and Methodologies. Marcel Dekker, USA 1998, p. 23), Dunphy's formulations were neutralized to determine if neutralizing the pH would stabilize the nucleic acids. However, nucleic acids stored in any of the Dunphy's media could not be detected.

27. These experiments demonstrate that Dunphy's media is not suitable for the storage of nucleic acids, in any variation. Digene's UCMI formulations are suitable.

28. I declare further that all statements made on information and belief are believed to be true, and, further, that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and such willful false statements may jeopardize the validity of the instant patent specification or any patent issuing thereon.

Respectfully submitted,

Date: March 25, 2003

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# Curriculum Vitae

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**University Education:**

**Graduate, 1976-1979** Department of Genetics, Trinity College, Dublin, Ireland.
**Ph.D., 1980.** Research project: Investigation of cell size and cell division control in *Saccharomyces cerevisiae*.

**Undergraduate, 1972-1976** University College, Dublin, Ireland.
**B.Sc., Honors 1976.** Microbiology (major), Biochemistry (minor).
Research project: Characterization of an α-amylase of *Pseudomonas saccharophila*.

**Professional Positions:**

**Senior Vice President and Chief Scientific Officer**, since 2000. Digene Corporation, Gaithersburg, Maryland 20878.
Report directly to company President and CEO. Responsibilities include: key role in company policy decision-making at the executive committee level; speaking at scientific meetings worldwide as an acknowledged expert on human papillomaviruses and genetic testing; instigating and supervising basic scientific research; collaborating with scientists worldwide in studies published in prestigious peer-reviewed journals; evaluating Digene's position on intellectual property; evaluating new technology in other laboratories for possible licensing or other use by Digene; representing Digene and its technology at business meetings worldwide.

**Vice President, R&D, and Scientific Director, 1990-1999.**
Responsibilities included: supervision and guidance of up to 40 scientists, long-range scientific planning for the company, review of detailed research plans, assurance of quality results, and timely achievement of company R&D goals. Principal areas of research focus were the development of diagnostic nucleic acid probe tests for a broad range of human infectious diseases, cancers, and inherited disorders. Other responsibilities included the planning and coordination of clinical studies, U.S. Food and Drug Administration submissions, and interactions with high-level biomedical consultants and collaborators from universities and other companies.

**Lecturer, 1999.** Zanvyl Krieger School of Arts and Sciences, Johns Hopkins University, Montgomery County Center, Rockville, MD 20850.
Designed and taught a new course in the history of medical diagnostics for candidates for the M.A. in Biotechnology.

**Adjunct Associate Professor**, 1989-present. Department of Pathology, Georgetown University Medical School, Washington, DC 20007.
Research efforts focused on human papillomaviruses, with particular emphasis on diagnostic applications, and on molecular mechanisms of carcinogenesis in human keratinocytes. Other projects involved the study of tumor suppressor genes and their use as markers for cancer prognosis.

**Scientific Director, Corporate Research**, 1989-1990. Life Technologies, Inc., Gaithersburg, Maryland. Studied *in vitro* transcription, transgenic animals, and other model systems of interest to research scientists for the purpose of generating research reagents.

**Section Head of Advanced Molecular Diagnostics**, 1984-1989. Life Technologies, Inc. Gaithersburg, Maryland. Investigated medical and molecular aspects of the human papillomavirus.

**Research Scientist**, 1982-1984. University of California at Santa Barbara. Investigated regulation and organization of *S. cerevisiae* genes involved in cell cycle control.

**Research Scientist**, 1980-1982. University of California at San Diego. Performed quantitative computer analyses of protein regulation during the cell cycle of *S. cerevisiae*, using two-dimensional gel electrophoresis.

**Honors And Other Professional Activities:**

High Technology Council of Maryland Award for Biotechnology Product of the Year 2000, awarded to the Hybrid Capture® II HPV DNA Test.

American Venereal Disease Association A.V.D.A. Achievement Award 1994, presented in recognition of outstanding contributions toward the control of sexually transmitted diseases.

Primary author of cell cycle paper in Nature, 1984.

Senior author of papers in JAMA, 2000, detailing the role of HPV in cervical cancer screening.

Editorial board member of IVD Technology and of Clinical and Diagnostic Virology.

Scientific and medical reviewer for: Obstetrics and Gynecology, Science, Journal of Clinical Microbiology, Journal of General Virology, Clinical and Diagnostic Virology, and others.

Peer reviewer for the National Institutes of Health, since 1986.

Life Technologies, Inc., David L. Coffin Award for Technical Innovation, for developing the FDA approved HPV test ViraPap®, 1989.

Life Technologies, Inc., David L. Coffin Patent Award, for human papillomavirus 56 nucleic acid hybridization probes and methods for employing same, US Patent No. 4,908,306.

Irish Department of Education Ph.D. Scholarship Recipient, 1976-1979.

**National Clinical Trials:**

Co-principal investigator for HPV QC Group in the NCI ALTS study to investigate alternatives in women's health care for managing cervical disease. Contract NCI-CN-55044-07, awarded 1995.

**Federal Research Grants:**

Principal Investigator for Contract N44-AI-85335, "Rapid Detection and Typing of HSV DNA." SBIR Phase II grant from NIAID, awarded May, 1998.

Principal Investigator for Contract N43-AI-45214, "Rapid Detection and Typing of Herpes Simplex virus (HSV) DNA in Clinical Specimens." SBIR Phase I grant from NIAID, completed 1996.

Subcontract MA-5623-26 with Microbiological Associates, Inc., "Assays to Detect and Type Human Papillomavirus DNA in Cervical Lavage Samples." Completed 1995.

**Patents:**

US patent nos. 4,849,331; 4,849,332; 4,849,334; and 4,908,306 for the use of HPV types 35, 43, 44, and 56 in diagnostic testing.

US patent nos. 5,981,179 and 6,027,897 and Australian patent no. 711130 for CAR target amplification technology.

Australian patent no. 673813 for Hybrid Capture® technology.

Other patents pending for Hybrid Capture® technology.

**Memberships:**

American Society for Microbiology (since 1980)

Pan American Group for Rapid Viral Diagnosis (since 1986)

American Association of Clinical Chemistry (since 1991)

International Committee on HPV Nomenclature (1986-1991)

**International Conferences**

*Dr. Lörincz has been an invited speaker at many international conferences, a list of which is available on request.*

**Departmental Seminars**

*Dr. Lörincz has been an invited speaker at many departmental seminars, a list of which is available on request.*

**Managerial Experience:**

- Head of several scientific teams, with full responsibilities for project planning, budgets, hiring, promotions, data analyses, presentations, publications, etc. Principal investigator for numerous clinical studies. As a member of the executive staff of Digene, I am intimately involved in setting overall company objectives and policies.
- Head of several multi-disciplinary strategic planning teams involving R&D, Regulatory Affairs, Marketing and Sales, Development, and Manufacturing.
- Director of Intellectual Property for Digene Corporation, 1990-1994. Prepared patent applications with assistance of attorneys.

- Played a major role in preparing several PMA applications for Life Technologies' and Digene's HPV testing kits. Presented data to FDA panels, leading to successful approval of the ViraType® and Hybrid Capture® kits for detecting and typing HPV DNA.

- Key member of the Executive Committee directing a successful initial public offering of Digene Corporation on NASDQ in May, 1996, and a secondary offering in October, 1997.

## SELECTED PUBLICATIONS

*Dr. Lörincz has 72 peer-reviewed scientific publications prior to 1995, a list of which is available on request. A list of peer-reviewed publication since 1995 follows:*

Schiffman, M.H., N.B. Kiviat, R.D. Burk, K.V. Shah, R.W. Daniel, R. Lewis, J. Kuypers, M.M. Manos, D.R. Scott, M.E. Sherman, R.J. Kurman, M.H. Stoler, A.G. Glass, B.B. Rush, I. Mielzynska, and **A.T. Lorincz** (1995) Accuracy and interlaboratory reliability of human papillomavirus DNA testing by Hybrid Capture. J. Clin. Microbiol. 33:545-550.

Cox, J.T., **A.T. Lorincz**, M.H. Schiffman, M.E. Sherman, A. Cullen, and R.J. Kurman (1995) Human papillomavirus testing by hybrid capture appears to be useful in triaging women with a cytologic diagnosis of atypical squamous cells of undetermined significance. Am. J. Obstet. Gynecol. 172(3):946-954.

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Tsukui, T.; Hildesheim, A.; Schiffman, M.H.; Lucci, J., III; Contois, D.; Lawler, P.; Rush, B.B.; **Lorincz, A.T.**; Corrigan, A.; Burk, R.D.; Qu, W.; Marshall, M.A.; Mann, D.; Carrington, M.; Clerici, M.; Shearer, G.M.; Carbone, D.P.; Scott, D.R.; Houghten, R.A.; Berzofsky, J.A. (1996) Interleukin 2 production *in vitro* by peripheral lymphocytes in response to human papillomavirus-derived peptides: correlation with cervical pathology. Cancer Res. 56(17):3967-3974.

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Attachment A

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Kessis, T.D., R.J. Slebos, W.G. Nelson, M.B. Kastan, B.S. Plunkett, S.M. Han, **A.T. Lörincz**, L. Hedrick, and K.R. Cho (1993) Human papillomavirus 16 E6 expression disrupts the p53-mediated cellular response to DNA damage. Proc. Natl. Acad. Sci. USA 90:3988-3992.

Sherman, M.E., M.H. Schiffman, **A.T. Lorincz**, M.M. Manos, D.R. Scott, R.J. Kurman, N.B. Kiviat, M. Stoler, A.G. Glass, and B.B. Rush (1994) Towards objective quality assurance in cervical cytopathology: correlation of cytopathologic diagnoses with detection of high-risk human papillomavirus types. Am. J. Pathol. 102:182-187.

Attachment B

## INVITED SPEAKER
## INTERNATIONAL CONFERENCES

1. Bay Area Yeast Meeting. August 3, 1983. Berkeley, California.
2. Origin of Female Genital Cancer. April 14-17, 1985. Cold Spring Harbor, New York.
3. Workshop on Mechanisms of Transformation by Papillomaviruses. February 18-19, 1986. Bethesda, Maryland.
4. Colposcopy, Cervical and Vulvar Pathology and Gynecologic Laser Surgery Conference. April 4-10, 1986. Sarasota, Florida.
5. Human Papillomaviruses and Cervical Carcinoma. Second International Conference. October 27-29, 1986. Chicago, Illinois.
6. Human Papillomaviral Infection and Lower Genital Tract Neoplasia. May 7-9, 1987. Atlanta, Georgia.
7. HPV Workshop - Type Consensus Meeting. March 22-23, 1988. New York, New York.
8. Human Papillomaviruses and Squamous Carcinoma. Third International Conference. October 24-26, 1988. Chicago, Illinois.
9. Impact of HPV Testing on Cervical Cancer Screening and Diagnosis. National Cancer Institute Sponsored Conference. February 2, 1989. Rockville, Maryland.
10. Colposcopy, Cervical and Vulvar Pathology and Gynecologic Laser Surgery Conference. February 27-March 5, 1989. Sarasota, Florida.
11. UCLA Conference on Papillomaviruses. March 11-18, 1989. Taos, New Mexico.
12. An Update: Human Papillomavirus Infection. April 14, 1989. Lenexa, Kansas.
13. Fifth Annual Clinical Virology Symposium. April 30-May 3, 1989. Clearwater Beach, Florida.
14. Thirtieth Annual Meeting of the Japanese Clinical Cytology Society. June 14-16, 1989. Tokyo, Japan.
15. Colposcopy, Cervical and Vulvar Pathology and Gynecologic Laser Surgery Conference. November 5-12, 1989. Sarasota, Florida.
16. Human Papillomavirus Infections—A Postgraduate Course. October 21-22, 1989. Washington, DC.
17. Diagnosis and Treatment of Vulvar, Vaginal and Cervical Disease - A Postgraduate Course. October 27-28, 1989. Washington, DC.
18. National Meeting of the Canadian Association for Clinical Microbiology and Infectious Diseases. November 26-30, 1989. Montreal, Canada.
19. Workshop on Development of STD Diagnostics for Resource-Poor Settings. February 7-8, 1990. Rosslyn, Virginia.
20. Sixth Meeting of the Scandinavian Society for Gynecological Medicine. September 6-8th, 1990. Mariehamn, Finland.
21. International Symposium on Diagnosis of Sexually Transmitted Diseases. August 16-17, 1991. Uppsala, Sweden.
22. Fourth International Conference on Human Papillomaviruses and Genital Carcinoma. September 17-19, 1990. Chicago, Illinois.
23. Second IARC Workshop on HPV and Cervical Cancer, November 25-28, 1991. Brussels, Belgium.
24. Fifth International Conference on Human Papillomavirus. October 25-28, 1992. Chicago, Illinois.
25. St. Joseph's Institute of Laboratory Medicine Symposium. April 29, 1993. London, Ontario, Canada.
26. Twelfth Annual High Technology R&D Trade Fair. May 10-11, 1993. Arlington, Virginia.
27. 8th World Congress of Cervical Pathology and Colposcopy. May 12-16, 1993. Chicago, Illinois.
28. 1993 U.K. Wellcozyme Users Conference. June 17-18, 1993. St. Albans, England.

29. Steering Committee Meeting of the International Biological Study on Cervical Cancer. October 2, 1993. Baltimore, Maryland.
30. The American Society for Colposcopy and Cervical Pathology, in joint sponsorship with The Society of Canadian Colposcopists. March 22-26, 1994. Orlando, Florida.
31. 2nd International Congress of Papillomavirus in Human Pathology. April 6-8, 1994. Paris, France.
32. Novel Amplification Technologies for DNA/RNA-Based Diagnostics. April 20-22, 1994. San Francisco, California.
33. First Congress on Papillomavirus of the Catholic Cancer Center. May 7, 1994. Seoul, Korea.
34. The Feasibility of Genetic Technology to Close the HIV Window in Donor Screening (US FDA workshop) September 26-28, 1994. Silver Spring, Maryland.
35. Nucleic Acid-Based Technology: Revolution in Clinical Diagnosis, Applications and Research. November 7-9, 1994. Amsterdam, The Netherlands.
36. Nucleic Acid-Based Technologies: Current Challenges, Future Strategies, and End User Perspectives. May 31-June 2, 1995. San Francisco, California.
37. Murex Users' Meeting. June 7-8, 1995. London, United Kingdom.
38. Eleventh Meeting of the International Society for STD Research, August 27-30,1995. New Orleans, Louisiana.
39. X Congresso Brasileiro - II Congresso Latino Americano de Patologia do Trato Genital Inferior e Colposcopia. September 20-24, 1995. Sao Paulo, Brazil.
40. Workshop organized by Murex Diagnostica GmbH. October 12, 1995. Zurich, Switzerland.
41. XVth Asian and Oceanic Congress of Obstetrics and Gynecology. October 15-20, 1995. Bali, Indonesia.
42. Gene Quantification: Diagnosis, Monitoring & Drug Development. February 26-27, 1996. San Diego, California.
43. VIII Curso Internacional de Cancer Cervico Uterino y Lesiones Premalignas. March 7-9, 1996. Mexico City, Mexico.
44. Gene Detection: Diagnostic Technology for Infectious Agents and Human Genetic Diseases. May 2-3, 1996. Coronado, California.
45. 9th World Congress of Cervical Pathology and Colposcopy. May 12-16, 1996. Sydney, Australia.
46. EUROGIN-WHO International Joint Experts Meeting "Cervical Cancer Screening and New Developments. June 17-19, 1996. Geneva, Switzerland.
47. State of Maryland Department of Health and Mental Hygiene Office of Maternal Health and Family Planning. August 9, 1996. Annapolis, MD.
48. Advances in Nucleic Acid Amplification & Detection. September 18-19, 1996. Amsterdam, The Netherlands.
49. IV Simposio International e III Jornada Baiana de Patologia do Trato Genital Inferior e Colposcopia. October 3-6, 1996. Salvador, Brazil.
50. The American Society for Microbiology, New York City Branch, & St. John's University. November 1, 1996. Jamaica, New York.
51. XIII Latin American Microbiology Congress. November 5-9, 1996. Caracas, Venezuela.
52. Workshop on Cervical Cancer Screening Program. November 6-7, 1996. Juquei, SP, Brazil.
53. EUROGIN-WHO 3rd International Congress on Lower Genital Tract Infections and Neoplasia: Future Challenges and Strategies. March 25-28, 1997. Paris, France.
54. 15th Annual Reproductive Health Update, co-sponsored by the Maryland Department of Health and Mental Hygiene Office of Maternal Health and Family Planning, Anne Arundel Community College, and Planned Parenthood. April 25, 1997. Arnold, MD.
55. Symposium on HPV Infection and Cervical Cancer. May 11, 1997. Seoul, Korea.
56. HPV workshop. May 16, 1997. Taipei, Taiwan, R.O.C.
57. XV FIGO World Congress of Gynecology and Obstetrics. August 3-8, 1997. Copenhagen, Denmark.

58. HPV Testing: European Perspectives on Cervical Neoplasia Prevention, Prognosis and Management. November 13-15, 1997. Geneva, Switzerland.
59. European HPV Clinical Summit Meeting. January 29-30, 1998. Vienna, Austria.
60. IV Reunión Nacional de Colposcopia y Patologia Cervical. February 19-21, 1998. Guadalajara, Mexico.
61. Gene Quantification: Clinical Applications and Drug Development. March 30-April 1, 1998. San Diego, CA.
62. Biennial Meeting, American Society for Colposcopy and Cervical Pathology. March 30-April 2, 1998. Scottsdale, AZ.
63. ASCP/CAP Spring Meeting. April 4-8, 1998. Los Angeles, CA.
64. 8th European Course on HPV-Associated Pathology. April 22-24, 1998. Munich, Germany.
65. DNA/RNA Diagnostics. May 19-21, 1998. Washington, DC.
66. Microbial-Linked Diseases: Shifting the Pathogenic Paradigm. June 25-26, 1998. San Diego, CA.
67. Human Papillomavirus Infections and Cervical Cancer. July 7-11, 1998. Montreal, Canada.
68. Simposio Internacional sobre HPV: IV Curso de Atualizacao em Patologia do Trato Genital Preparatorio para Concurso de Qualificacao em Colposcopia. September 3-4, 1998. Belo Horizonte, Brazil.
69. IIIer Congreso Lainoamericano y IIdo Congreso Paraguayo de Patologia del Tracto Genital Inferior y Colposcopia. September 7-11, 1998. Asuncion, Paraguay.
70. 17th International Papillomavirus Conference. January 9-15, 1999. Charleston, SC.
71. INCGC - Consensus Conference on Cervical Cancer Screening and Management. January 28-31, 1999. Tunis, Tunisia.
72. HPV Summit 1999: New Approaches to the Detection and Elimination of Cervical Cancer. February 8-10, 1999. Chamonix, France.
73. Centers for Disease Control and Prevention and American Cancer Society External Consultants' Meeting: Prevention of Genital HPV Infection and Sequelae. April 13-14, 1999. Atlanta, GA.
74. 11th International Meeting of Gynaecological Oncology. May 8-12, 1999. Budapest, Hungary.
75. 4th Scientific Meeting on Primary and Secondary Prevention of Gynecological Cancer. May 14-16, 1999. Thessaloniki, Greece.
76. 13th Meeting of the International Society for Sexually Transmitted Diseases Research. July 11-14, 1999. Denver, CO.
77. Reproductive Health '99. September 22-25, 1999. New York, NY.
78. 1999 ASCP/CAP Fall Meeting. September 25-30, 1999. New Orleans, LA.
79. 10th World Congress of Cervical Pathology & Colposcopy. November 7-11, 1999. Buenos Aires, Argentina.
80. North American Sexual Health Management Symposium. November 21-23, 1999. New York, NY.
81. Cervical and Breast Cancer in the Next Millenium. December 3-6, 1999. Mexico City, Mexico.
82. XI Encontro de Atualização em Patologia do Trato Genital Inferior e Colposcopia – Cervicolp' 2000. March 23-25, 2000. Sao Paulo, Brazil.
83. EUROGIN 2000: Global Challenge of Cervical Cancer Prevention. April 4-9, 2000. Paris, France.
84. ASCP/CAP Spring Meeting. April 9-12, 2000. Boston, MA.
85. Clinical Implications Conference 1: "Role of Human Papillomavirus in Cervical Neoplasia." April 28-29, 2000. Chicago, IL.
86. 26th National Meeting of the Clinical Ligand Assay Society. May 31-June 2, 2000. Boston, MA.
87. Meeting of the Pathological Society of Great Britain and Ireland. July 12-14, 2000. Nottingham, UK.
88. 7th International Meeting of Genital Tract Pathology & Colposcopy. October 25-30, 2000. Belo Horizonte, Brazil.

Attachment C

**INVITED SPEAKER**
**DEPARTMENTAL SEMINARS**

1. Heidelberg Cancer Research Center, Heidelberg, Germany. November, 1985.
2. Columbia Hospital for Women, Washington, DC. December, 1985, 1986, and 1991.
3. Fred Hutchinson Cancer Research Center, Seattle, Washington, July, 1988.
4. Johns Hopkins Medical Institutions, Baltimore, Maryland, November, 1990.
5. University of New Hampshire, Department of Microbiology. October, 1991.
6. Sharp Memorial Hospital OB/GYN Department, San Diego, California, November 11, 1993.
7. Prodia Laboratory, Jakarta, Indonesia, May 3, 1994.
8. Bio-Check Laboratories Ltd. Pathology, Diagnostic Virus, and Gynecology Departments, Taipei, Taiwan, R.O.C., May 5, 1994.
9. University College Hospital Virology Department, London, United Kingdom, June 16, 1995.
10. John Radcliffe Infirmary Pathology Department, Oxford, United Kingdom, June 17, 1995.
11. National Cancer Hospital Cytology Department, Oslo, Norway, October 10, 1995.
12. Columbia Hospital for Women Pathology Department, Washington, DC, October 24, 1995.
13. Associated Regional University Pathologists (ARUP), Salt Lake City, UT, February 28, 1996.
14. Washington Hospital Center, Transplant Surgery Department, March, 1996.
15. Health Insurance Plan of New York, Jericho, NY, April 24, 1996.
16. Friedrich Schiller University Department of Obstetrics and Gynecology, Jena, Germany, May 8, 1996.
17. Unilab KPT/ Murex Diagnostica GmbH, HPV workshop for gynecologists/venerologists/ pathologists/virologists, Budapest, Hungary, May 10, 1996.
18. Long Island Jewish Medical Center Gynecology Department, New York, NY, June 5, 1996.
19. Washington Gynecological Society, Washington, DC, January 8, 1997.
20. Hyundei Medical Center, Seoul, Korea, May 10, 1997.
21. Seoul National University, Seoul, Korea, May 12, 1997.
22. Papanicolaou Institute, Buenos Aires, Argentina, July 14-16, 1997.
23. Doctors' meeting convened by Murex Central Europe, Vienna, Austria, November 17, 1997.
24. One seminar and one grand rounds, for the departments of Gynecologic Oncology, Biochemistry & Molecular Genetics, and Infectious Diseases at the University of Alabama at Birmingham, December 9-10, 1998.
25. Maryland Bioscience Alliance, High Technology Council of Maryland, Rockville, MD, January 21, 1999.
26. University of Rochester Research Symposium on Human Papillomavirus Infections from the Bench to the Bedside, Rochester, NY, April 30, 1999.
27. Women's Health Task Force Meeting, Washington, DC, February 29-March 1, 2000.
28. Maryland Bioscience Alliance Cancer Forum, High Technology Council of Maryland, Rockville, MD, March 22, 2000.
29. Gynecologic Cancer Translational Research Retreat, Chantilly, VA. May 5-6, 2000.
30. 18th Annual Reproductive Health Update for the Maryland Department of Health, Annapolis, MD. May 19, 2000.
31. Georgetown University Department of Pathology, Washington, DC. May 25, 2000.
32. Cleveland Clinic Foundation, Cleveland, OH. June 30, 2000.

33. University of Medicine and Dentistry of New Jersey, Scotch Plains, NJ. October 13, 2000.